ORIGINAL ARTICLE

Incidence and prevalence of cryptogenic fibrosing alveolitis in a Norwegian community

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Abstract This study assesses the incidence and prevalence of cryptogenic fibrosing alveolitis (CFA) in a well-defined and stable Norwegian population of 250 000 inhabitants during a period of 15 years. We conducted a file survey of all patients (n = 376) aged 16 years or older with a clinician's diagnosis of pulmonary fibrosis (ICD 8: 517 and ICD 9: 515 and 516). Cases with a history of exposure to fibrogenic agents or with collagen vascular disease were excluded and the remaining 158 cases were defined as CFA. The average annual incidence of hospitalised CFA was 4.3 per 100 000. No change was observed in the annual incidence during the 15-year study period. The prevalence was 19.7 and 23.9 per 100 000 by 31.12. 1991 and by 31.12. 1998, respectively. The incidence increased considerably and significantly with age. No significant gender differences were observed. The lack of gender differences and the increase with age were also found when the diagnosis of CFA was exclusively based on cases with hospital file records of breathlessness, bilateral crackles and bilateral shadows on chest radiograph.

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Keywords cryptogenic fibrosing alveolitis; incidence; prevalence; population-based.

INTRODUCTION

Cryptogenic fibrosing alveolitis (CFA) is by definition a progressive pulmonary fibrosis without a known cause. The disease usually presents with dyspnoea, bilateral crackles and bilateral radiographic shadowing (1,2). The American Thoracic Society and the European Respiratory Society (3) recommend the use of thin-section computer tomography and eventually video-assisted or open lung biopsy (3) in the diagnosis of CFA but these have until recently not been used routinely in Norway or Great Britain (2,4).

Data on the frequency and geographic distribution of CFA are sparse (5), and there is only one population-based study regarding the prevalence of CFA from the Nordic countries (6). We studied the incidence and prevalence of physician-diagnosed and hospitalised CFA in a well-defined adult population in Norway.

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METHODS

Population

Bergen hospital district is located on the south-west coast of Norway. The district incorporates the city of Bergen and the surrounding 14 municipalities. According to the Norwegian national census data, the district had 226 659 inhabitants aged 16 or older in 1984, 244 347 in 1992 and 254 999 in 1999. Seventy per cent of the population lived in Bergen, which is Norway's second largest city. About 98% of the population were Caucasians (7). Villages and rural areas constitute the remaining part of the district. The annual in- and out-migration is below 3%.

Health-care system

All specialised health care and all second and third line health services for the population are provided by two hospitals with a total of 1400 beds. The only department of thoracic medicine is located at Haukeland University hospital while Deaconess hospital has a department of internal medicine. Persons living in the health district who by chance are hospitalised in other districts are

usually referred back to the local hospital as soon as they can be transported. Health care is free of charge and health insurance universal.

Discharge diagnoses

At the departments, discharge diagnoses were made under the supervision of a consultant in thoracic medicine. During the study period (1984–1998), there was a consensus on the use of the diagnostic criteria for CFA advocated by Turner-Warwick *et al*. (1): progressive dyspnoea, crackles on auscultation and bilateral shadowing on chest X-ray with no exposure to a known fibrogenic agent.

Inclusion criteria

Potential cases over the age of 16 were identified in the patient registers by the following physician diagnoses (ICD 8): 517 (alia pneumonia chronica interstitialis), 517.00 (fibrosis interstitialis diffusa pulmonum essentialis), 517.01 (fibrosis pulmonis), 517.09 (pneumonia chronica interstitialis alia NUD) (8). ICD 8 was used in Norway from 1984 to 1989. Since 1990 ICD 9 has been used and thus we included patients with ICD 9 diagnoses 515 (post-inflammatory pulmonary fibrosis), 516.3 (idiopathic fibrosing alveolitis), 516.8 (interstitial pneumonia) and 516.9 (unspecified alveolar and parietoalveolar pneumonopathies) (9).

Case ascertainment

A computer-aided search of the hospital registers was carried out to find all patients who had been hospitalised between 1.1.1984 and 31.12.1998. An additional manual search of the patient register of the internal medicine department at Deaconess hospital was performed for 1984 – 1987 because here patient data had only been computerised since 1.1.1988.

For our study, we translated and modified a registration form previously used by Scott and co-workers (10). It incorporated demographic data, smoking history, relevant symptoms, signs and lung function variables and applied diagnostic procedures.

Two physicians abstracted data from the patient records. Cases with file documentation of the following factors were excluded: pulmonary fibrosis associated with collagen vascular disease, intake of cytotoxic and other potentially fibrogenic drugs, radiotherapy and exposure to asbestos as well as silica. Cases with sarcoidosis or allergic alveolitis from exposure to moulds or birds were also excluded.

Data analysis

The prevalence of CFA was estimated using the cases that were alive by 31.12.1991 and by 31.12.1998. Incident cases were all patients diagnosed during the 15 years from 1.1.1984 until 31.12.1998. The calculation of incidence and prevalence was based on the national census data (7). Death of patients was verified by the Norwegian population register, which is updated daily.

Data were entered from the registration form onto a personal computer using Access version 1997 (11) and analysed with SPSS version 9.0 (12). Results of lung function tests were registered as raw data and converted to percentage predicted values using the European Community for Steal and Coal equations (13).

Gender differences, differences between clinical symptoms of prevalent and incident cases as well as the yearly incidences were tested by the chi-square statistic. Gender and age trends were calculated using logistic regression and were adjusted for the increase in the general population. Because of multiple comparisons, the level of significance was defined as $P < 0.01$ (14).

RESULTS

General

Altogether 376 cases were identified with an ICD number suggestive of pulmonary fibrosis. Thirteen patient files could not be found in the archives and 30 patients had no indication of pulmonary fibrosis whatsoever and must have been misdiagnosed or coded incorrectly at discharge. Collagen vascular disease was present in the files of 36 cases and other known causes of pulmonary fibrosis were found in 69 cases. These causes were exposure to asbestos, dusts, birds, radiation therapy or treatment with chemotherapy and other potentially fibrogenic drugs. Forty-one patients had been referred from other hospital districts and 29 had been diagnosed before 1.1.1984. Of the remaining 158 incident cases, 97 had died and 61 were alive by 31.12.1998. The latter number represents the prevalent cases in 1998. By 31.12. 1991, there were 48 prevalent cases. Four hundred and sixty-five hospital admissions for CFA were registered between 1984 and 1998. One hundred and eleven new cases had their first admission to Haukeland hospital and 47 to Deaconess hospital. Deceased cases with CFA in Bergen hospital district had in average 3.3 (range 1 – 11) hospital admissions during a median survival of 4.1 years.

Demographic characteristics and smoking habits

The mean age at diagnosis of the incident cases was 69.2 (range 22 – 93) years and 45% were men (Table 1). The mean age at diagnosis of prevalent cases by 31.12.1998

Table 1. Gender, smoking habits and age of incident and prevalent cases of CFA in Bergen Hospital District

	Incident cases 1984 – 1998	Prevalent cases 31.12.1998
n	158	61
Men (%)	45	34
Smoking habits (%)		
Current smokers (%)	22	25
Ex-smokers	28	23
Never smokers	41	49
Unknown	9	3
Age at diagnosis, mean (SD), (years)	69.2 (17)	59.2 (19)

was 59.2 (range 22 – 90) and 34% were men. Only six men and three women (6% of all cases) were diagnosed with CFA 16 – 34 years old. Sixty-five men and 84 women, altogether 83% of the cases, were diagnosed when they were over 54 years old (Fig. 1). Smoking habits did not differ between incident and prevalent cases (Table 1). More men (68%) than women (36%) were ever smokers ($P < 0.005$). No significant differences in smoking habits were observed between prevalent and deceased cases ($P = 0.22$).

Clinical characteristics

Dyspnoea was the most common symptom recorded in the files. Crackles on auscultation were recorded in two-thirds of the cases and almost nine out of 10 had bilateral shadowing on chest radiograph (Table 2).

Table 2. Percentages[a] of incident and prevalent cases of CFA with dyspnoea, crackles, bilateral interstitial shadows on chest radiograph, restrictive spirometric pattern and reduced TLCO

	Incident cases 1984 – 1998	Prevalent cases per 31.12.1998
n	158	61
Dyspnoea	87	79
Bilateral basal crackles	77	62
Bilateral interstitial shadows	91	89
Restrictive spirometric pattern[b]	55	46
TICO < 80% of predicted	83	80

[a]Information was available on dyspnoea, crackles, chest radiograph, spirometry and diffusion capacity in 151, 157, 158, 97, 65 of the incident cases and in 57, 60, 61, 46, 35 of the prevalent cases

[b]Defined as forced vital capacity (FVC) < 80% of predicted and forced expiratory volume in 1 s (FEV_1)/FVC > 0.7.

Spirometry was recorded in 61% and diffusion capacity in 41% of the incident cases and in 75 and 57% of the prevalent cases. Spirometry was performed in 84% of the cases below the age of 75 years and in 36% of the cases above ($P < 0.002$). Diffusion capacity was measured in 64 and 15% ($P < 0.001$) of the respective groups. Fewer deceased than prevalent cases had performed TLCO

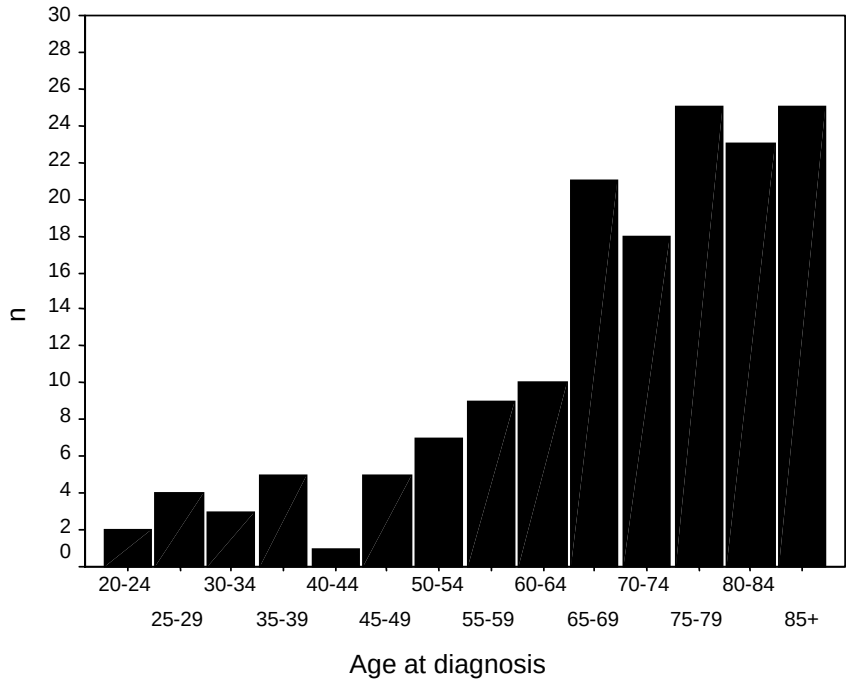

Fig. 1. Age of incident cases with CFA in 5 year groups.

($P = 0.002$) and simple spirometry ($P = 0.012$). A restrictive lung function pattern defined as forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) > 0.7 and FVC < 80% of expected was present in half of the cases that had performed the test. Reduced diffusion capacity was present in 80% of the cases (Table 2).

Incidence and prevalence

The median number of incident cases was 11 per year. The number of new cases per year varied from 5 to 17 during the study period (Fig. 2) yet the differences were not significant ($P = 0.47$).

The average annual incidence of hospitalised CFA was 4.3 per 100 000 inhabitants over 16 years of age. In men it was 4.0 (95% CI: 3.1–4.9) and in women 4.6 (95% CI: 3.7–5.6) per 100 000 (Table 3). The prevalence was 23.4 per 100 000 inhabitants by 31.12.1998 (95% CI: 14.9–33). The prevalence of hospitalised CFA per 100 000 by 31.12.1991 was 19.7 (95% CI: 14.1–25,3). The difference between the prevalence in 1991 and 1998 was not significant ($P = 0.31$).

In the logistic regression, there was a significant increase of both incidence and prevalence with age ($P < 0.01$). A non-significant female predominance in incidence and prevalence was found taking all age groups together ($P = 0.71$). There was no significant interaction between age and gender ($P = 0.54$).

Incidence and prevalence did not differ significantly ($P = 0.79$) between inhabitants of the city of Bergen and the surrounding municipalities. Median survival of incident cases was 4.1 years (95% CI: 3.1–5.2).

In 98 cases of CFA dyspnoea, bilateral crackles and bilateral radiographic shadowing were recorded in the hospital files. Calculating the incidence based on these cases it was 2.3 and 3.0 per 100 000 per year in men and

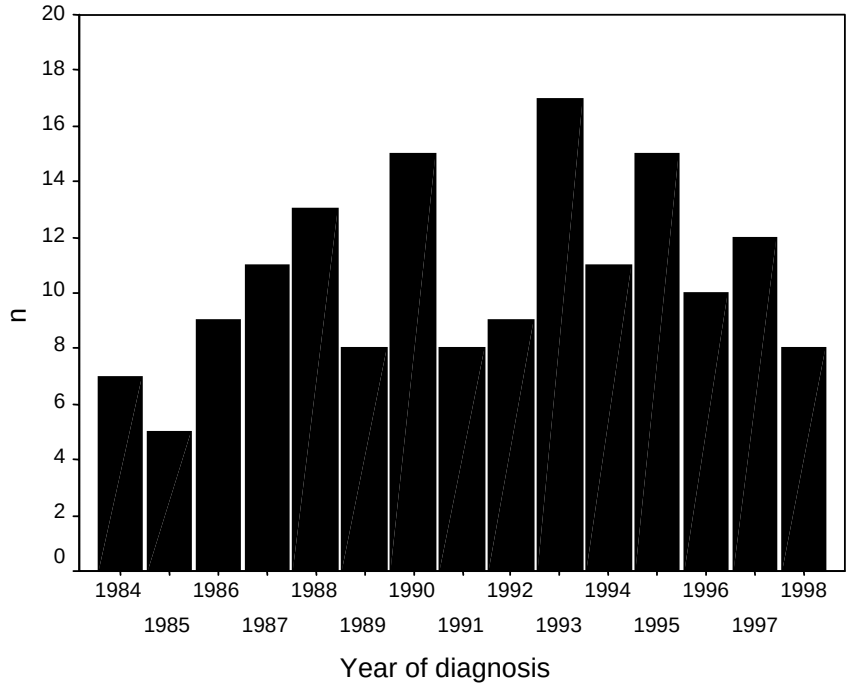

Fig. 2. New cases with CFA in Bergen Health District diagnosed between 1984 and 1998.

Table 3. Hospitalised cases and incidence of CFA per 100 000 inhabitants during 1984–1998 in Bergen Hospital District. Cases and incidence with the three recorded criteria dyspnoea, crackles and bilateral shadows on chest radiograph

Age (years)	Hospitalised cases						Hospitalised cases with three recorded criteria					
	Men		Women		Total		Men		Women		Total	
	n	Incidence	*n*	Incidence	*n*	Incidence	*n*	Incidence	*n*	Incidence	*n*	Incidence
16–34	6	0.8	3	0.4	9	0.6	2	0.3	0	—	2	0.1
35–54	10	1.6	8	1.4	18	1.6	4	0.7	4	0.7	8	0.7
55–74	22	6.1	36	8.6	58	7.5	13	3.6	25	6.0	38	4.9
75+	33	30.6	40	19.3	73	23.3	22	20.5	28	13.6	50	15.9
Total	71	4.0	87	4.6	158	4.3	41	2.3	57	3.0	98	2.7

Table 4. Hospitalised cases and prevalence by 31.12.1998 of CFA per 100 000 inhabitants in Bergen Hospital District. Cases and prevalence with the three recorded criteria dyspnoea, crackles and bilateral shadows on chest radiograph

Age (years)	Hospitalised cases						Hospitalised cases with 3 recorded criteria					
	Men		Women		Total		Men		Women		Total	
	n	Prevalence	*n*	Prevalence	*n*	Prevalence	*n*	Prevalence	*n*	Prevalence	*n*	Prevalence
16–34	5	10.3	3	6.4	8	8.4	2	4.1	0	—	2	2.1
35–54	7	16.1	8	19.3	15	17.6	2	4.6	4	9.6	6	7.1
55–74	6	24.8	14	52.1	20	39.2	3	12.4	7	26.1	10	19.6
75+	3	35.2	15	96.7	18	74.9	2	23.4	9	58.0	11	45.8
Total	21	16.8	40	30.7	61	23.4	9	7.2	20	15.3	29	11.4

women, respectively (Table 3). The prevalence using the same diagnostic criteria was 7.2 per 100 000 in men and 15.3 per 100 000 in women (table 4). Incidence and prevalence increased with age ($P < 0.01$) but gender differences ($P = 0.48$) were not observed.

DISCUSSION

In a community study in Norway over a time period of 15 years, we observed an annual incidence of hospitalised CFA of 4.3 and a prevalence of 23.4 per 100 000 inhabitants aged 16 and older. There were no overt differences between men and women. A marked increase with age was present in both incidence and prevalence.

Methodological considerations

The frequency of CFA in this population is estimated for patients requiring hospitalisation. This will underestimate the incidence and prevalence in the general population, as less symptomatic cases are not referred to a hospital in the health district. The inclusion of patients was based on consultant physicians' ICD diagnoses. The validity of the clinical diagnosis and coding of CFA is controversial. A study from the UK showed a high accuracy of ICD 9 code 516.3 (idiopathic fibrosing alveolitis) but low reliability of other fibrosis-related diagnoses (15). Meanwhile, a study from the U.S.A. (16) concluded that the agreement between clinical diagnoses of CFA and death certificate data was low. On the other hand, physicians' diagnoses are a well-established and practical tool in epidemiological research, and have been used in earlier studies of CFA (17). Furthermore, we initially included a broad range of ICD diagnoses to reduce underestimation of the frequency of CFA.

In a proportion of our cases, not all the typical clinical findings of CFA were recorded in the files. It has earlier been noted that the presence of symptoms and signs in CFA is variable (18,19). Turner-Warwick *et al*. (1) found dyspnoea in 92% and bilateral crackles in 96% and the chest radiograph was normal in 2% of 220 patients admitted to a tertiary referral centre in the U.K. In the British Thoracic Society Study (2), the chest radiograph was normal in 2% of the CFA cases and 10% had no dyspnoea on exertion. The variability of the clinical findings in previous as well as in our study is probably a consequence of the inclusion of different histological subgroups of CFA and the patients may have been at different stages of the disease. Demedts *et al*. (5) recommended to diagnose and classify CFA or idiopathic pulmonary fibrosis according to the guidelines of the American Thoracic Society and the European Respiratory Society (3). Here the term idiopathic pulmonary fibrosis is reserved for cases with the typical pattern of usual interstitial pneumonia on high-resolution computed tomography and eventually surgical lung biopsy specimens. Since our study started long before high resolution computed tomography was available in our hospitals and before the consensus was obtained we had to rely on the clinical practice at that period of time. Therefore, our estimates of incidence and prevalence apply to CFA as defined by clinical criteria (1). Thus, the whole spectrum of idiopathic interstitial pneumonias is included and our results are not limited to patients with usual interstitial pneumonia (3). To which extent the frequency of CFA will change when high-resolution computed tomography becomes more widely used requires further investigation.

In our retrospective study, results of simple lung function tests were available in about two-thirds of our cases. We have few lung function data in patients above the age of 75 years probably because it is more difficult to obtain acceptable test results in the elderly. However, in the prospective British Thoracic Society study of CFA (2) spirometry was recorded in 96% and diffusion capacity in 75% of cases.

Incidence estimates

The incidence of CFA varies between 0.9 and 9.1 per 100 000 in different countries (Table 5). These large

Table 5. Annual incidence and prevalence per 100 000 inhabitants of CFA from population-based studies in six countries

Country	Incidence	Prevalence
USA (22)	9.1	16.7
Japan (23)	—	10.0
UK (10)	—	6.0
Spain[a] (24)	1.3	—
Czech Republic (25)	0.9	12.1
Finland (6)	—	16–18
Norway (present study)	4.0	23.4

[a]Idiopathic interstitial pneumonias.

differences have been attributed to diagnostic imprecision, lack of internationally accepted classifications and weaknesses of study design (5,20,21). The incidence in Bergen lies between that found in a region in southern Spain and in Moravia and Selesia, Czeck Republic on one side and in New Mexico, U.S.A. on the other side (Table 5).

In the comprehensive population-based study from Bernalillo county, New Mexico (22) all new cases of interstitial lung diseases were registered over a 2-year period in a population of nearly half a million inhabitants. All pulmonary and primary-care physicians as well as internists in this region were informed in writing about the register and asked to submit all patients with interstitial lung diseases. A rather unspecific clinical or pathological diagnosis was the basis for all referrals and was also used to establish a final diagnosis in the register. The incidence of CFA was 10.7 per 100 000 per year in men and 7.4 in women while the average incidence rates in Bergen Hospital District are only half as high. One possible reason for this difference can be the longer observation period of 15 years in the present study, which was only 2 years in the study from New Mexico (22). The number of new cases of CFA varied in Bergen more than threefold from year to year. Given our longer surveillance period, the real differences of the incidence between the two geographical areas may have been less. Another factor contributing to the higher incidence could be that physicians in Bernalillo County referred milder cases of CFA not necessarily requiring hospitalisation. Finally, one has to take into account that environmental factors may influence the occurrence of CFA. Bernalillo County is a major mining area (22) while Bergen hospital district has no mining industry and only little wood and metal industry.

Prevalence estimates

The prevalence of CFA varied in previous studies between 6 and 18 per 100 000 (Table 5). Our prevalence of 24 per 100 000 is comparatively high, most likely because we included not only cases with usual interstitial pneumonia but also other types of idiopathic interstitial pneumonias with a longer survival. In the nationwide study from Finland (6), thin-section computer tomography was preformed in a majority and lung biopsies in nearly one-third of the patients thus reducing the number of cases with an idiopathic interstitial pneumonia other than usual interstitial pneumonia.

A spirometry survey (26) conducted in a random sample of the population aged 18–73 years of Bergen and 11 surrounding communities showed a restrictive spirometric pattern ($FEV_1/FVC > 0.70$ and $FVC < 80\%$) in 9% of men and 7% of women and the prevalence increased heavily with age. The causes of this rather high prevalence of a restrictive spirometric pattern are not known. In any case, CFA can only explain a small fraction of the occurrence of the restrictive spirometric pattern. This large discrepancy between the prevalence of hospitalised CFA and the restrictive spirometric pattern in the community should be further examined.

In the national mortality statistics CFA (ICD 8: 517, ICD 9: 515, 516.3) was registered as primary cause of death in 893 patients in Norway between 1982 and 1995 (27) rendering a death rate of 1.4 per 100 000 per year. No gender difference was observed. The Norwegian Patient Register (28) has registered 3239 admissions for CFA between 1990 and 1996. This represents an admission rate of 9.3 per 100 000 per year for the whole country. Given our prevalence of 24 per 100 000, the yearly admission rate in Bergen hospital district would be 19 per 100 000 inhabitants above the age of 16 years, when each patient had in average 3.3 admissions during a median survival of 4.1 years. This is somewhat higher than the national hospital admission rate.

Gender

In their community study, Coultas and co-workers (22) found that CFA had a male-to-female ratio of 1.5. Hubbard *et al*. (29) in a case–control study reported a male-to-female ratio of 2.2. On the other hand, Hodgson and co-workers (6) in their recent nationwide study from Finland found no gender differences in the prevalence of CFA. In a German registry, even a slight female predominance was registered (30). We did not find a predominance of men in the incidence and prevalence of CFA in this Norwegian population but rather a female predominance in the prevalence estimate taking all age groups together.

The lack of a male predominance in our study could be related to the fact that few men in Bergen hospital district work in polluting industry (31). Smoking is most probably a risk factor for CFA (30,32). Norwegian women are among the heaviest smokers in the world (34) and 36% of the women in our study were current or ex-smokers. Thus, the high number of smoking women in

our study could partially explain the high fraction of female cases. Another possible explanation is that women if exposed to an equivalent amount of tobacco smoke may be at higher risk to develop respiratory disease than men. Accordingly, Langhammer and co-workers (35) found that Norwegian women had a higher frequency of respiratory symptoms than men given the same burden of tobacco smoke.

The observation in earlier studies of a male predominance has given rise to the hypothesis that CFA could be caused by occupational hazards, namely dusts from wood and metal (27). Since we do not find a clear male predominance our data cannot support this hypothesis.

Age

A prominent finding in our study is the increase of CFA with age. The age trend was similar for men and women as well as for prevalent and incident cases. This confirms CFA as a disease of the elderly (3,21).

The mean age at diagnosis of our incident cases was 69 years, which is similar to that observed in the 588 patients (67 years) of the British Thoracic Society Study (2). In the study by Coultas and co-workers (23), the mean age was 61 years probably reflecting referral bias in favour of younger patients.

The prevalent cases in our study are in average 10 years younger than the incident cases. This is probably due to a high fraction of young patients with a long survival among the prevalent cases.

The lower mean age at diagnosis of the prevalent than of the incident cases in our study is due to a higher fraction of living cases that were diagnosed at relatively young age. These meet the inclusion criteria of the present study but probably do not have usual interstitial pneumonia, which usually has a shorter survival.

In summary, the incidence of hospitalised CFA is lower in this population-based study from Norway than in New Mexico, U.S.A. but higher than in other European countries and Japan. The prevalence is similar to that observed recently in Finland. Probably, diagnostic differences explain a part of these variations. Incidence and prevalence increase considerably with age. No gender difference was observed. This is in contrast with previous findings of a male dominance of CFA, which has been ascribed to occupational exposure to various fibrogenic agents. Further studies into the occupational history of women as well as men in our patient population and international comparisons are warranted to pursue the hypothesis that environmental hazards play a role in the aetiology of CFA.

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